PROTOCOL

A randomised controlled trial to assess the immunogenicity, safety and reactogenicity of standard dose versus fractional doses of COVID-19 vaccines (Pfizer-BioNTech or Moderna) given as an additional dose after priming with Pfizer-BioNTech or AstraZeneca in healthy adults in Australia

Protocol Number: 81764
Protocol Version 2.0 and date:
20th December 2021

NCT05228730

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

This clinical trial is not sponsored by any pharmaceutical company or other commercial entity

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PROTOCOL SYNOPSIS

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<tr><td rowspan="9">TRIAL DESCRIPTION</td><td colspan="2">This clinical trial will be a single blind*, randomised study to determine the reactogenicity and immunogenicity of booster doses of SARS-CoV-2 vaccines in adults. Both fractional and standard doses will be tested.</td></tr>
<tr><td>Primary vaccine</td><td>Booster vaccines</td></tr>
<tr><td rowspan="4">Pfizer-BioNTech (BNT162b2)</td><td>1. Pfizer-BioNTech (BNT162b2 or Comirnaty®) Standard dose (30μg) n=100</td></tr>
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<tr><td rowspan="4">AstraZeneca (ChAdOx1-S, or Vaxzevria®)</td><td>5. Pfizer-BioNTech (BNT162b2 or Comirnaty®) Standard Dose (30μg) n=100</td></tr>
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<tr><td>8. Moderna (mRNA-1273 or Spikevax®) Fractional Dose (20μg)** n=100</td></tr>
<tr><td colspan="3">* Subjects and assessors will be blinded to the vaccine allocation for one month (28 days) following administration, and laboratory staff will be blinded to vaccine allocation associated with specimens.
**Recent data from UK/USA indicate that reactogenicity is an issue for full dose Moderna (100μg) boosters, hence we are using fractional doses for this vaccine. Currently the recommended standard booster dose is 50μg.</td></tr>
<tr><td>OBJECTIVES</td><td colspan="2"><u>Primary objectives</u> –
• To assess and compare the immune response measured as binding antibodies (IgG ELISA) following standard versus fractional doses of Pfizer or Moderna vaccine given as single additional doses in adults 18 years or older in Australia who have been primed through previous vaccination with Pfizer or AstraZeneca vaccines. (Timepoint – 28 days post vaccination)</td></tr>
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	• To assess the rate and severity of reactogenicity within one-week post-booster for each group (Timepoint – 7 days post vaccination) Secondary objectives - (timepoint –12 months) • To compare the duration of immunity, both humoral and cellular, over 12 months for fractional vs standard booster doses of the vaccines listed. • To evaluate the different priming capacities of Pfizer and AstraZeneca vaccines. • To evaluate the safety of the booster dose regimens.
OUTCOMES AND OUTCOME MEASURES	Outcomes: • Reactogenicity will be measured using the accepted standardised method for evaluation of systemic and local side effects following vaccination using a structured questionnaire for seven days post-vaccination. All moderate or severe reactions will be reviewed by study staff. • All solicited adverse events (AE) will be collected for 7 days, all unsolicited AE will be collected for 28 days, and all medically attended AE will be collected for 3 months. SAE will be collected throughout the follow up period of 12 months. Adverse events of special interest will be categorised as per CEPI guidelines (1) • Antibodies (binding and functional) and cellular immune responses will be measured (see outcome measures for details) Reactogenicity • Reactogenicity will be measured by recording the following parameters: o Local reaction - pain, tenderness, erythema/redness, induration/swelling o Systemic – Nausea/vomiting, headache, fatigue/malaise/myalgia, arthralgia Immunology endpoints *Binding antibody* – These will be evaluated using the commercial Euroimmun S1 IgG ELISA on serum collected at 4 timepoints (baseline, 28 days, 6 months, and 12 months). For all subjects, the 28 days post-vaccination sample will be assayed within four weeks of collection. *Functional antibody* – All samples will be assayed using the GenScript cPass SARS-CoV-2 Neutralization Antibody detection kit for both WT and Delta variant RBD antigen. *Neutralizing antibody* - A fraction of samples (20%) will be assessed using a SARS-CoV-2 assay undertaken at the PDI, Melbourne. Testing will be at 4 timepoints for Wuhan strain and 2 Variants of Concern.

	Cellular immunity - Cellular immunity will be assessed on a 40% subset of samples collected at three timepoints: baseline, 28 days, and 12-months post-vaccination as follows: • *QuantiFERON Human IFN-γ* SARS-CoV-2 (Qiagen) will be performed using whole blood. • Assays performed on PBMCs will include IFN-*γ* Elispot, intracellular cytokine assays (flow cytometry) and multiplex cytokine assays.
TRIAL POPULATION	Participants will be adults aged 18 years or older who have received two doses of either Pfizer-BioNTech (BNT162b2, or *Comirnaty®*) or AstraZeneca (ChAdOx1-S, or *Vaxzevria®*) 6 to 9 months before entering this study; in line with ATAGI recommendations (2). There will be no upper age limit. Participants will be recruited from staff, their families and acquaintances at the Murdoch Children's Research Institute, the Royal Children's Hospital, the PDI and if necessary, the greater Melbourne area. 100 participants will be recruited per group, and there will therefore be 800 participants in total. Procedures will be implemented to ensure participants of all ages (aged 18 and above) are included and that there is an even age distribution in each group (<50 and ≥50 years).
DESCRIPTION OF SITES ENROLLING PARTICIPANTS	This will be a single site study with all participants enrolled at RCH
DESCRIPTION OF INTERVENTIONS	The interventions being studied are as follows:
	Pfizer-BioNTech (BNT162b2, or *Comirnaty®*) Standard Dose
	Pfizer-BioNTech (BNT162b2, or *Comirnaty®*) Fractional Dose
	Moderna (mRNA-1273, or *Spikevax®*) Standard Dose
	Moderna (mRNA-1273, or *Spikevax®*) Fractional (20μg) Dose
TRIAL DURATION	The recruitment period will be approximately 4 months. Each participant will have six visits over a follow-up period of 12 months following their immunisation visit.
PARTICIPANT DURATION	Participant duration will be 12 months, and there will be six visits. The DSMB will review participant safety data monthly. Binding antibody ELISA results (Euroimmun) will be reviewed by the DSMB for all participants who receive a fractional dose, and compared with those who received a full dose. They will review all cases that do not meet the seroresponse definition (p38-39). The DSMB will decide if participants will be offered a further booster dose.

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
ANOVA	Analysis of Variance
AR	Adverse Reaction
ATAGI	Australian Technical Advisory Group on Immunisation
BRF	Biobank Registration Form (MCRI)
CEPI	Coalition for Epidemic Preparedness Innovations
CRF / eCRF	Case Report Form / electronic Case Report Form
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IM	Intramuscular
MCRI	Murdoch Children's Research Institute
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
PBMC	Peripheral blood mononuclear cells
PDI	Peter Doherty Research Institute
PI / CPI	Principal Investigator / Coordinating or Chief Principal Investigator
PI	Product Information (available for an approved drug or device)
QA	Quality Assurance
QC	Quality Control
RGO	Research Governance Office
RCH	Royal Children's Hospital (Melbourne)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SoA	Schedule of Assessments
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
SST	Serum separator tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
UAR	Unexpected Adverse Reaction
USM	Urgent Safety Measure

INVESTIGATOR AGREEMENT

I have read the protocol entitled "A randomised controlled trial to assess the immunogenicity, safety and reactogenicity of standard dose versus fractional doses of COVID-19 vaccines (Pfizer-BioNTech or Moderna) given as an additional dose after priming with Pfizer-BioNTech or AstraZeneca in healthy adults.".

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki, and the good clinical practice guidelines adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments].
Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee, with the exception of medical emergencies.
I will ensure that trial staff fully understand and follow the protocol, and evidence of their training is documented on the trial training log.

Name	Role	Signature and date
Prof Kim Mulholland	Sponsor-investigator	
Dr Claire von Mollendorf	Co-Principal Investigator	

1. ADMINISTRATIVE INFORMATION

1.1. Trial registration

1.1.1. Trial registry

The trial will be registered on ClinicalTrials.gov prior to trial commencement.

1.2. Sponsor

On behalf of the Sponsor, MCRI, the Sponsor-Investigator leading the trial, will undertake and oversee those Sponsor responsibilities delegated by the Sponsor. The delegated Sponsor responsibilities are documented in the study file.

Trial Sponsor	MCRI
Contact name	Kathryn Bright – kathryn.bright@mcri.edu.au
Address	Flemington Road, Parkville
Sponsor-Investigator	Prof Kim Mulholland

1.3. Expected duration of study

The expected duration of the study is 24 months which includes preparation and reporting. The recruitment period is anticipated to be 3 months and all participants will be followed up for 12 months.

1.4. Contributorship

Name	Summary of contribution	Affiliation
Prof Kim Mulholland	Sponsor-investigator	MCRI
A/Prof Paul Licciardi	Investigator - Immunology	MCRI
Dr Claire von Mollendorf	Investigator – Medical/Epidemiology	MCRI
Prof Nigel Crawford	Investigator - Advisor/ Chair of ATAGI/ Immunization specialist	MCRI
Prof Kanta Subbarao	Investigator - Immunology	PDI
A/Prof Siddhartha Mahanty	Investigator – Infectious Disease Specialist	PDI
Dr Lien Anh Ha Do	Investigator - Virology	MCRI
Dr Cattram Nguyen	Investigator - Statistics	MCRI
Eleanor Neal	Investigator – Data Management/Analysis	MCRI
Kathryn Bright	Investigator – Melbourne Project Manager	MCRI
Emma Watts	Investigator – Project Manager	MCRI
Helen Thomson	Investigator – Project Manager	MCRI

1.5. Stakeholder involvement

The Coalition for Epidemic Preparedness Innovations (CEPI) is a foundation that takes donations from public, private, philanthropic, and civil society organisations to finance independent research projects to develop vaccines against emerging infectious diseases. CEPI is providing funding for this study. CEPI has reviewed this protocol, and they have been involved in the development of the project.

2. INTRODUCTION AND BACKGROUND

2.1. Trial rationale and aim

Additional or booster doses of Covid-19 vaccines are currently being used in a number of countries with minimal data regarding optimal timing, target groups, duration of protection and safety. In addition, there is currently ongoing inequity in vaccine availability in many low- and middle-income countries with vaccine coverage in many countries in Africa at <1% of the eligible population. There are however a number of critical outstanding questions related to the use of booster doses. These include optimal timing, particularly after priming with inactivated vaccines that provide shorter duration of protection, and the potential use of fractional dosage. We have chosen three sites (Australia, Mongolia, and Indonesia) which together will be suitable to answer these questions.

Due to the rapidly developing field much of the data had been presented in various WHO meetings, but is currently unpublished (Appendix 1). Currently the most comprehensive published booster study is the UK-based multi-site CovBoost study (3). This study demonstrated the use of fractional doses of Pfizer vaccine to be very close to equivalent in patients primed with AstraZeneca or Pfizer vaccines. This protocol covers the component to be studied in Australia and will focus on booster regimens relevant to Australia and not previously studied elsewhere in the world.

2.2. Background

It is becoming clear that all Covid-19 vaccines are not equal. While all the EUL listed products effectively prevent severe and fatal Covid-19, prevention of mild or asymptomatic infection is variable, and the duration of protection seems limited and highly variable. As most low- or middle-income countries are struggling to access sufficient Covid-19 vaccines for their population, it may seem inappropriate to be examining options for boosting immunity. We are proceeding with this project for the following reasons:

1. Some countries that have achieved high coverage with inactivated vaccines with little impact on overall disease rates have begun programs of heterologous (e.g., UAE, Mongolia) or homologous (e.g., Chile) boosting, without a strong scientific basis for the schedules chosen. Guidance is needed on how this should be achieved.
2. Countries that have begun vaccination early with support from COVAX have usually started by vaccinating front line health workers (e.g., Indonesia). With minimal vaccination of the general population, health workers have been exposed to large numbers of infected patients and increasing numbers of Covid-19 illness and death among health care workers have led to informal attempts to boost immunity for this group (4).
3. The use of fractional doses as boosters has been shown to produce similar boosting to full doses for two vaccines (Johnson & Johnson (5) and Moderna (6)), and an unpublished study from Thailand (Appendix 1) and recent data from UK (3) have shown a similar effect with half dose Pfizer vaccine. The use of fractional doses for booster doses and potentially primary series could save large volumes of vaccine, potentially freeing up vaccine for communities that currently lack access. Recent guidelines in US and UK recommend the use of half dose (50μg) for Moderna booster doses, while follow-up of earlier studies indicate that a 20μg dose is likely to be adequate as a booster (7-9).

2.3. Risk/Benefit assessment

2.3.1. Known potential risks

This study will provide safety data of the booster regimens being studied and will collect safety data for fractional doses of the booster vaccines.

The safety profiles of the vaccines being tested are well described (see Appendix 2 - Product information sheets).

<u>Possible lower efficacy of fractional booster dose</u>

Participants who receive a fractional dose are at a small risk of not receiving sufficient vaccine to protect against COVID-19 infection.

Risks associated with sample taking

Participants may experience discomfort and/or localised bruising from venepuncture and there is a small risk of fainting. The total volume of blood drawn over a 12-month period will be up to 114mls which is safe in otherwise healthy adults.

Allergic reactions

Allergic reactions may occur to any of the constituents of the booster vaccine. These may range from mild to severe but are usually rare. Patients should be questioned regarding allergic reactions to any vaccines in the past. All participants will have previously received two doses of a Covid-19 vaccine.

Reactogenicity

It is possible that participants might experience more reactogenicity if their booster vaccine is different to the vaccine used in their primary two dose schedule. This is compensated for by the expected superior immunogenicity seen with heterologous boosting schedules.

2.3.2. Known potential benefits

Booster doses of Covid-19 vaccines are available to all adults in Australia and there may be no direct benefits for participants enrolling in this study, apart from the opportunity to learn their antibody response following the booster. In addition, the fractional dose booster may be shown to be equally effective with less reactogenicity. Participants will receive a heterologous boost which may be shown to be superior to a homologous boost. Studies have shown that mRNA boosting potentially offers superior immunogenicity for individuals primed with AstraZeneca (10).

While early reports from Israel and the US confirm the effectiveness of a third dose of Covid-19 vaccine in some heterologous or homologous regimens, there is only limited data on the use of fractional dosage in heterologous regimens. This study will provide data crucial to designing optimal vaccine strategies in Australia and other countries that have used Pfizer-BioNTech (NT162b2, or *Comirnaty®*) or AstraZeneca (ChAdOx1-S, or *Vaxzevria®*) as primary two dose regimens.

2.3.3. Assessment of potential risks and benefits

Pfizer and Moderna vaccines are currently available to the general population as a booster The trial component is to examine administration of fractional doses. The risk of fractional doses is the potential for lower effectiveness, while the use of heterologous boosters poses the risks of increased reactogenicity and uncertain effectiveness. These factors are balanced against the potential benefits of heterologous boosting which include preservation of vaccine through the use of fractional doses, and potentially superior immunogenicity and broader protection. It should be noted that the risks and benefits from homologous boosting also remain unclear.

3. TRIAL OBJECTIVES AND OUTCOMES

3.1 Objectives

3.1.1 Primary objective

- The primary objectives of the study are to: -To assess and compare the immune response measured as binding antibodies (IgG ELISA) following standard versus fractional doses of Pfizer or Moderna vaccine given as a single additional dose to adults 18 years or older in Australia who have been primed through previous vaccination with Pfizer or AstraZeneca vaccines. (Timepoint – 28 days post vaccination)
- To assess the rate and severity of reactogenicity within one-week post-booster for each schedule evaluated.

3.1.2 Secondary objectives

The secondary objectives are to: -

- To compare the immunogenicity, both humoral and cellular, over 12 months following fractional and standard booster doses of the vaccines listed. .
- To evaluate the different priming capacities of Pfizer and AstraZeneca vaccines
- To evaluate the safety of the booster dose regimens

3.2 Outcomes

3.2.1 Primary outcomes

Immune response

Binding antibody – These will be evaluated using the commercial Euroimmun S1 IgG ELISA on all serum samples collected at 4 timepoints (baseline, 28 days, 6 months, and 12 months). Assays for all subjects will be completed within 4 weeks of sample collection. For subjects who receive a fractional dose, assays on the 28 days post-vaccination sample will be performed within two weeks of collection and reviewed by the DSMB.

Reactogenicity

Reactogenicity will be measured using the accepted standardised method to evaluate systemic and local side effects following vaccination using a structured questionnaire for days post-vaccination as outlined in Table 1 below.

Table 1. Grading system for evaluation of systemic and local side effects following vaccination (11).

Local Reaction to Injectable Product				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness[a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling[b]	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
[a] The measurement should be recorded as a continuous variable in addition to grading the measured local reaction at the greatest single diameter. [b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.				
Systemic (General)				
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) Oral or axillary temperature	38.0 – 38.4	38.5 – 38.9	39.0 – 40	>40
Nausea/vomiting	No interference with activity or 1 – 2 episodes /24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization

		interference with activity		
Fatigue/Malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia (muscle pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia (joint stiffness)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
In addition, appearance of the following potential signs of myocarditis/pericarditis will prompt referral for cardiology evaluation: Chest pain, dyspnoea, painful breathing, palpitations, or syncope.				

3.2.2 Secondary outcomes

Immunogenicity

Functional antibody – All samples at all timepoints will be assayed using the GenScript cPass SARS-CoV-2 Neutralization Antibody detection kit for both WT and Delta variant RBD antigen.

Neutralizing antibody - A fraction of samples (20%) will be assessed using a SARS-CoV-2 microneutralisation assay undertaken at the PDI, Melbourne. Assays will be done at all four timepoints to the WT (vaccine) strain and for 2 Variants of concern.

Cellular immunity - Cellular immunity will be assessed on a subset of 40% of participants, with samples collected at three timepoints: baseline, 28 days, and 12-months post-vaccination as follows:

- *QuantiFERON Human IFN-γ* SARS-CoV-2 (Qiagen) will be performed using heparinised whole blood
- Peripheral blood mononuclear cells (PBMCs) will also be isolated by density gradient centrifugation within 12 hours of collection and stored in liquid nitrogen at MCRI. Assays performed will include IFN-γ Elispot, intracellular cytokine assays (flow cytometry) and multiplex cytokine assays.

Safety

- All solicited adverse events (AE) will be collected for 7 days, all unsolicited AE will be collected for 28 days, and all medically attended AE will be collected for 3 months. SAE will be collected throughout the follow up period of 12 months

4 TRIAL DESIGN

4.1 Overall design

This clinical trial will be a single blind, randomised study to determine the immunogenicity and reactogenicity of booster doses of SARS-CoV-2 vaccines in adults. Both fractional and standard doses will be tested.

The groups are described below. The trial intervention will be a single booster dose of vaccine: -

Primary vaccine	Booster vaccines
Pfizer-BioNTech (BNT162b2, or *Comirnaty®*)	1. Pfizer-BioNTech (BNT162b2, or *Comirnaty®*) Standard dose
	2. Pfizer-BioNTech (BNT162b2, or *Comirnaty®*) Fractional dose
	3. Moderna (mRNA-1273, or Spikevax®) Standard Dose
	4. Moderna (mRNA-1273, or Spikevax®) Fractional Dose
AstraZeneca (ChAdOx1-S, or *Vaxzevria®*)	5. Pfizer-BioNTech (BNT162b2, or *Comirnaty®*) Standard Dose
	6.Pfizer-BioNTech (BNT162b2, or *Comirnaty®*) Fractional Dose
	7. Moderna (mRNA-1273, or Spikevax®) Standard Dose
	8. Moderna (mRNA-1273, or Spikevax®) Fractional Dose

The trial intervention will be given 6-9 months after the primary vaccine. This is in line with ATAGI recommendations for booster vaccine doses which allows booster doses from 5 months onwards (2). The groups size will be 100 individuals with an even spread of participants above and below 50 years in each group. The trial will be single site.
The trial will be single blind. The participants and those evaluating reactogenicity will be blinded to the vaccine allocation for the first 28 days following vaccination. After that, both the clinical investigators and potentially participants will be aware of their investigational product allocation. Immunologists and laboratory staff will remain blinded to the investigational product allocation.

4.2 Justification for dose

This project is designed to evaluate the potential use of fractional dose and heterologous booster regimens for individuals who have previously received two doses of Covid-19 vaccine. The fractional dose has advantages for the individual and the broad community. At an individual level, the likelihood of moderate adverse reactions is reduced by the use of a fractional dose. Existing data suggests that immunogenicity and effectiveness will be maintained, but this will be evaluated early in the project and if immunogenicity proves to be inadequate this will be addressed according to the recommendations of the DSMB. At a national and global level, the approach carries the potential to greatly expand the availability of Covid-19 vaccine, helping to correct the inequity that currently characterises the global Covid-19 situation.

4.3 Trial population

The trial population will be adults 18 years and older who have received two doses of Covid-19 vaccines, either Pfizer-BioNTech (BNT162b2, *Comirnaty®*) or AstraZeneca (ChAdOx1-S, *Vaxzevria®*) within the previous 6 to 9 months. There will be no upper age limit.
Procedures will be implemented to ensure participants of all ages (aged 18 and above) are included and that there is an even age distribution in each group.

4.4 Eligibility criteria

If informed consent is granted, study staff will ensure that all the eligibility criteria are met. Potential participants must meet all the inclusion criteria and none of the exclusion criteria to be eligible.

4.4.1 Inclusion criteria

Each participant must meet all the following criteria to be enrolled in this trial:

1. Have completed two doses of Pfizer-BioNTech or AstraZeneca vaccines with the recommended schedule 6 months prior to the date of enrolment
2. Willing and able to give written informed consent
3. Aged 18 years or above
4. Willing to complete the follow-up requirements of the study

Note that subjects with comorbidities other than those listed below as contraindications will be included. Pregnant women or women who may become pregnant will be included.

4.4.2 Exclusion criteria

Potential participant meeting any of the criteria below will be excluded from this trial:

1. Received 3 doses of COVID-19 vaccine
2. Received 2 doses of COVID-19 less than 6 months prior to the start of the trial
3. Received a different Covid-19 vaccine not available in Australia
4. Currently on immunosuppressive medication or anti-cancer chemotherapy
5. HIV infection
6. Congenital immune deficiency syndrome
7. Has received immunoglobulin or other blood products in the 3 months prior to vaccination
8. Study staff and their relatives
9. Have a history of a severe allergic reaction to any COVID-19 vaccines or have a medical exception to receiving further COVID-19 vaccines
10. Cannot read or understand English

4.5 Lifestyle considerations

Not Applicable.

4.6 Screen failures

Screen failures are defined as participants who consent to participate in the trial but are found during screening procedures to be ineligible. They, therefore, do not receive the intervention and are not randomised. We anticipate that there will be very few screen failures due to the minimal inclusion/exclusion criteria.

4.7 Recruitment and identification of potential participants

The study will be advertised across the Melbourne Children's Campus (MCRI, Royal Children's Hospital, Royal Melbourne Hospital, Doherty Research Institute), Royal Melbourne Hospital, the Doherty Research Institute, the Parkville precinct and if necessary the broader Melbourne community. Study information (via email, healthcare facilities notice board and/or website/social media etc) will include an information sheet about the study and a link to the study website where they can evaluate their eligibility and obtain additional study details, such as the participant information sheet and consent form (PICF). The potential participant can register their interest and will be given the opportunity to talk with a member of the research team by phone or zoom if they have any further questions. A record of all potential participants will be recorded on a recruitment log. If the potential participant decides not to participate no identifying information will be retained.

4.8 Consent

Informed consent is a process that is initiated prior to the agreement to participate in the trial and continues throughout study participation. Discussion of risks and possible benefits of this vaccination will be provided to the potential participants prior to obtaining informed consent. Trial staff will go through the Informed Consent Form (ICF), which describes in plain language the trial interventions, the study procedures, and the risks and benefits of participation. The ICF will be HREC-approved and the potential participant will be asked to read and review the ICF. The trial staff will then explain the research study further and answer any questions that may arise.

Written documentation of informed consent is required prior to enrolment into the trial. The potential participant will sign and date the final page of the ICF. The trial staff will witness the consent, confirming that the trial has been fully explained and that participant understands the rationale for the trial and the trial processes. The potential participant will be informed that they are free to withdraw from the trial at any time. A copy of the ICF will be given to the potential participant.

5 INTERVENTION

5.1 Treatment arms

Treatment Arms	Route	Dose
1) Pfizer-BioNTech (BNT162b2, or *Comirnaty®*)	IM	Standard Dose - (30μg)
2) Pfizer-BioNTech (BNT162b2, or *Comirnaty®*)	IM	Fractional Dose - (15μg)
3) Moderna (mRNA-1273, or Spikevax®)	IM	Standard Dose - (50μg)
4) Moderna (mRNA-1273, or Spikevax®)	IM	Fractional Dose - (20μg)

5.2 Trial Intervention(s)

Pfizer BioNTech (BNT162b2) BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein. BNT162b2 encodes the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation and more closely mimic the intact virus with which the elicited virus-neutralizing antibodies must interact. mRNA vaccines use the pathogen's genetic code as the vaccine; this then exploits the host cells to translate the code and then make the target spike protein. The protein then acts as an intracellular antigen to stimulate the immune response. The mRNA is then degraded within days. The vaccine RNA is formulated in lipid nanoparticles (LNPs) for more efficient delivery into cells after intramuscular injection.

Moderna (mRNA-1273) COVID-19 Vaccine Moderna (mRNA-1273) encodes the S-2P antigen, consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1–S2 cleavage site. S-2P is stabilized in its prefusion conformation by two consecutive proline substitutions at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit. The lipid nanoparticle capsule is composed of four lipids and formulated in a fixed ratio of mRNA and lipid.

5.2.1 Description of trial investigational products

5.2.1.1 Trial Products

Active substance	The Pfizer-BioNTech COVID-19 vaccine, BNT162b2, encodes a P2 mutant spike protein and is formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA).
Trade or Generic name	Pfizer-BioNTech (BNT162b2, or *Comirnaty*®)
Dosage form	Liquid for injection – standard dose is 0.3ml containing 30μg; fractional dose is 0.15ml containing 15ug.
Route of administration	Intramuscular injection

Active substance	The Moderna vaccine, mRNA-1273 encodes the prefusion stabilized S protein of SARS-CoV-2 formulated in RNA-LNPs composed of 4 lipids and 1-monomethoxypolyethyleneglycol-2, 3-dimyristylglycerol with polyethylene glycol.
Trade or Generic name	Moderna (mRNA-1273, or *Spikevax®)*
Dosage form	Liquid for injection – standard dose for boosting is 0.25ml containing 50μg; fractional dose is 0.1ml containing 20ug.
Route of administration	Intramuscular injection

5.2.2 Dosage

The standard dose of Pfizer BioNTech COVID-19 vaccine is 30μg contained in 0.3ml of the diluted vaccine and is currently the standard dose that is used for a booster. A half dose is 15 μg contained in 0.15ml of the diluted vaccine. Each pack of the Pfizer BioNTech vaccine contains 195 vials with 5 full doses per vial (975 doses per pack). It is supplied with 0.9% sodium chloride diluent for injection plastic ampoules.

The full dose of Moderna COVID-19 vaccine (used for primary schedules) is 100 μg of mRNA in 0.5ml of the diluted vaccine. A half dose is 50 μg contained in 0.25ml of the diluted vaccine and is currently the standard booster for this vaccine in the US,UK and AU. A fractional dose will be 20 μg contained in 0.1 ml of the diluted vaccine Each pack of the Moderna vaccine contains 10 vials with 20 half doses or 50 fractional doses per vial and is a white to off white dispersion.

5.2.3 Dose modification

Dose modification is not permitted and must be given as per randomisation.

5.2.4 Storage, preparation, dispensing and administration of trial drug

All study vaccines will be stored at the vaccination clinic at RCH and will be stored in accordance with the manufacturers' recommendations. See below:

- The Pfizer BioNTech vaccine should be stored at -70°C +/- 10°C and has a shelf life of 6 months. Once thawed, the vaccine may be stored for 31 days at 2-8°C. Once thawed vaccines will be stored in the RCH vaccination clinic refrigerators.
- The Moderna vaccine can be stored for 7 months at -25ºC to -15ºC. It should not be stored or transported on dry ice or below -40ºC. Once thawed it should not be re-frozen and may be stored refrigerated at 2 °C to 8 °C protected from light for up to 30 days if not used (needle punctured). Chemical and physical stability of an unopened vial after removal from refrigerated conditions has been demonstrated for 12 hours at 8° to 25°C. Chemical and physical in-use stability has been demonstrated for 6 hours at 2 to 25 ºC after first puncture. It should not be re-frozen once thawed.

Vaccine accountability, storage, shipment, and handling will be in accordance with relevant SOPs and forms.

5.2.5 Product accountability

The trial vaccines will be stored in the Immunisation clinic at RCH. Vaccination nurses trained in administrating COVID-19 vaccines, will draw up the study vaccines each day and deliver them to the vaccination room. The study nurses will ensure that storage requirements are maintained. Study vaccines will be administered by unblinded vaccinators, who will maintain blinding such that those evaluating reactogenicity are kept blinded during the first month (28 days) post-vaccination.

The Immunisation clinic will maintain accurate records of the receipt of all trial vaccines, including dates of receipt. In addition, study nurses will keep accurate records regarding when and how much trial vaccine is dispensed and used for each participant in the trial. Reasons for departure from the expected dispensing regimen will be recorded. At the end of the trial, there will be final reconciliation of trial vaccine received, dispensed, consumed, and returned. Any discrepancies will be investigated, resolved, and documented by the trial team. Unused trial vaccines will be destroyed in compliance with applicable regulations.

Detailed information regarding product accountability will be provided in an SOP.

5.2.6 Excluded medications and treatments

There are no excluded medications or treatments apart from those associated with exclusions listed in section 4.4.2.

5.2.7 Concomitant therapy

Concomitant medications taken by participants during the study will be documented as part of the safety review procedures.

5.2.8 Discontinuation from trial intervention

See Section 7.5.

6 RANDOMISATION AND BLINDING

Once consent has been obtained, and following eligibility assessment, eligible participants will be recruited and randomised. Participants will be randomised 1:1:1:1 to one of the 4 intervention groups (*Comirnaty®* standard full dose, *Comirnaty®* fractional dose, *Spikevax®* standard half dose, *Spikevax®* fractional dose) stratified by the primary vaccine received (*Comirnaty®* or *Vaxzevria®*) and age (<50 and ≥50 years). A secure, password-protected web-based randomisation schedule will be provided by an independent statistician from the Melbourne Children's Trial Centre at the Murdoch Children's Research Institute. Blocked randomisation will be used with random blocks of permuted length. To ensure there are even numbers by primary vaccine and age group, participants will be recruited until the number required in each stratum has been reached.

40% of participants from each group will be included in the CMI subgroup analysis. The strata that will be used for CMI analysis will be identified at this time, and measures will be taken to ensure that the age strata (<50 and ≥50 years) are equally represented in this group. Only 10 CMI samples can be processed per day. We will therefore recruit the first 10 participants (5 in each of the age strata) who consent to participate in this substudy per day. Daily recruitment will be stopped once each subset is complete.

6.1 Concealment mechanism

Randomisation will be stratified according to age (<50 and ≥50 years)) and primary vaccine (*Comirnaty®* or *Vaxzevria®*). Using REDCap the participants will be randomised to one of four groups in a 1:1:1:1 allocation ratio. (see table below).

Study staff involved in administering the vaccine will use REDCap to receive the information on the participant's randomisation number and vaccine allocation so they will be aware of which vaccine the participant is receiving. The participants themselves will remain blinded to their vaccine allocation (until day 28 post vaccination). Study staff involved in assessing reactogenicity will be blinded to each participant's vaccine allocation until 28 days post vaccination, as this variable will be hidden in REDCap for blinded study staff. Study staff involved in assessing immunogenicity outcomes will remain blinded during the analysis of specimens.

Vaccines will be prepared out of sight of the participant and the blind will be maintained by applying masking tape over the vaccine syringe, so the study participant can't see the volume.

The four booster vaccines will be prepared daily by the RCH immunisation clinic and delivered to the vaccination room and stored in the vaccine fridge. Only the study staff responsible for randomisation and drawing up and checking the vaccine will be aware of which vaccine is given to each study participant.

Primary vaccine	Age	Booster vaccine	Dose given
Pfizer-BioNTech	Below 50	Pfizer-BioNTech	30µg
		Pfizer-BioNTech	15µg
		Moderna	50µg
		Moderna	20 µg
	Above 50	Pfizer-BioNTech	30µg
		Pfizer-BioNTech	15µg
		Moderna	50µg
		Moderna	20 µg
AstraZeneca	Below 50	Pfizer-BioNTech	30µg
		Pfizer-BioNTech	15µg
		Moderna	50µg
		Moderna	20 µg
	Above 50	Pfizer-BioNTech	30µg
		Pfizer-BioNTech	15µg
		Moderna	50µg
		Moderna	20 µg

6.2 Breaking of the trial blind

6.2.1 On trial

The study will be blinded for the first 28 days only. In the unlikely event that it becomes necessary to unblind during this period that decision will be taken by the PI, and the subject and physicians who may be caring for the subject will be made aware of the allocation.

7 TRIAL VISITS AND PROCEDURES

7.1 Schedule of assessments

	Visit 1 (day 0)	Visit 2 (day 1)	Visit 3 (day 7)	Visit 4 (day 28)	Visit 5 (3 mths)	Visit 6 (6 mths)	Visit 7 (12 mths)
Timing	Day 0	Day 1	Day 7	Day 28	3 months	6 months	12 months
Visit window			+ 3 days	+ 7 days	+/- 14 days	+/- 14 days	+/- 14 days
Informed consent	X						
Eligibility confirmation	X						
Randomisation	X						

Blood sampling	X			X		X	X
Vaccination	X						
Vital signs	X						
Issue diary card, ruler and thermometer	X						
Collect diary card			X				
Documentation of Solicited AE	X	X	X				
Documentation of unsolicited AE	X	X	X	X			
Documentation of medically attended AE	X	X	X	X	X		
Documentation of SAE	Throughout study period						
Documentation of confirmed COVID-19 infection	Throughout study period						

7.2 Description of procedures

7.2.1 Visit 1 (Day 0)

Informed consent must be signed by both participant and study doctor or nurse.
Participant eligibility must be confirmed prior to randomisation and on the same date as administration of the investigational product.

Eligibility must be confirmed by a study doctor or study nurse. Randomisation must be completed by the unblinded vaccinator who will document the participant's randomisation number on the enrolment log.

Study staff will administer a Visit 1 questionnaire documenting demographic information, height and weight, dates and type of primary COVID-19 vaccine, any comorbidities and concomitant medication.

The following vital signs will be recorded by a study doctor or study nurse prior to vaccination: temperature, pulse rate, respiratory rate, and blood pressure.
Prior to vaccination, for all participants, 5mL of blood will be collected and processed according to the SOP. CMI participants will have an additional 25ml collected and processed for Quantiferon analysis and PBMC separation and storage.

Following randomisation, the unblinded vaccinator will administer the applicable vaccine to the participant.

The following vital signs will be recorded by a study doctor or study nurse 15 minutes following vaccination: temperature, pulse rate, respiratory rate, and blood pressure.
Study staff will provide participant with reactogenicity diary card and instruct the participant on how to complete the diary card up to and including 7 days following vaccination.
Study staff will provide the participant with a thermometer and ruler and detailed instructions on how to use these for measuring temperature and potential erythema and induration. Study staff will provide the participant with a schedule of visit appointments and instruct the participant on how to contact the study staff in case of any SAE or symptoms suggestive of COVID-19.
Study staff will keep the participant under observation for minimum 15 minutes and document any immediate adverse events.

7.2.1 Visit 2 (Day 1)

Study staff will contact the participant by phone approximately 24 hours after vaccination to review and document adverse events.

7.2.2 Visit 3 (Day 7)

An in-person visit will be conducted one week after vaccination. Study staff will collect and review the diary card and document adverse events.

7.2.3 Visit 4 (Day 28)

An in-person visit will be conducted 28 days following vaccination. All Unsolicited Adverse Events will be documented. Study staff will also document any new information regarding solicited adverse events with onset up to 7 days following vaccination, such as resolution. The participant will be informed which vaccine they received based on entry into the CRF by an unblinded staff member.
For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 3mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection.

7.2.4 Visit 5 (3 Months)

Study staff will contact the participant by phone and document information on any medically attended AE or SAE.
Study staff will also document any new information regarding unsolicited adverse events with onset up to 28 days following vaccination, such as resolution.

7.2.5 Visit 6 (6 Months)

For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 3mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection.

7.2.6 Visit 7 (12 Months)

For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 3mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC

will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection. Participants who complete the 12-month study period will receive a gift. If they request, results of their tests will be shared and discussed with them by a member of the study team.

7.2.7 Unscheduled visits

If any participant develops symptoms of Covid-19, they will be instructed to contact the Study Team and to get a PCR test at the nearest facility. If the test is positive the Study Team will seek to obtain a specimen for virology, either residual from the specimen that tested positive, or an additional swab once the positive result is known. One month after the positive test a 5ml blood sample will be collected and serum stored for future serological analysis. The participant will otherwise continue with scheduled study visits. The virology sample will be transported for sequencing and analysis by the Microbiological Diagnostic Unit Public Health Laboratory (MDU) in Melbourne. The study team will maintain telephone contact daily with the participant for the course of his/her illness and fully document all telephone calls. With the subject's permission the Team will seek clinical data from the health care providers or hospital in the event that the subject becomes clinically ill.

7.2.8 Withdrawal of consent - participant withdraws from all trial participation

A participant has the right to withdraw from the trial at any time and for any reason and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the participant at any time in the interests of the participants' health and well-being. In addition, the participant may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator
- Ineligibility (either arising during the trial or retrospectively, having been overlooked at screening).
- Significant protocol deviation
- Participant non-compliance with study requirements

The reason for withdrawal will be recorded in the CRF. If the participant has an AE at the time of withdrawal, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved, stabilised or a non-trial related causality has been assigned.
If a participant withdraws from the study, storage of samples and data collected before their withdrawal will still be used in the analysis, unless the participant specifically requests otherwise.

7.2.9 Losses to follow-up

A participant will be considered lost to follow-up if he/she fails to return for two consecutive visits and is unable to be contacted by the trial staff. The following action must be taken if a participant fails to return to the clinic for a required trial visit:

- Trial staff will attempt to contact the participant within one week of the missed visit and reschedule the visit.

- Before a participant is deemed lost to follow-up, trial staff will make every effort to regain contact. Three telephone calls will be made, and two emails sent. All contact attempts will be documented in the participants DCF.
- If the participant continues to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

7.2.10 Replacements

Participants who have been randomised and enrolled may NOT be replaced.

7.2.11 Trial Closure

The end of the trial is the date of the last assay conducted on the last sample collected.

8 SAFETY MONITORING AND REPORTING

8.1.1 Definitions for use in trials involving investigational medicinal products

Participant-specific adverse events

Adverse events must be assessed to determine each of the following:

1. Seriousness
2. Relatedness (i.e., causal relationship)
3. Expectedness

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR): Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR): Any adverse event/adverse reaction that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect.

Note: Life-threatening refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. **Important medical events** that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in this definition should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected.

Safety issues (requiring expedited reporting)

The following definitions describe additional safety events that require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA:
Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact the continued ethical acceptability or conduct of the trial.
Comment: An SSI is a new safety issue or validated signal considered by the Sponsor in relation to the investigational medicinal product that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the investigational medicinal product, which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the investigational medicinal product.
Urgent Safety Measure (USM): A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This is a type of SSI that can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

8.2 Capturing and eliciting adverse event/reaction information

Participants will be asked to record local and systemic AEs for 7 days (and longer if symptoms persist at day seven, until resolution or stabilisation) following vaccination in the electronic or paper diary card (solicited AEs). Unsolicited AEs All local and systemic AEs occurring in the 28 days following vaccination observed by the Investigator or reported by the participant, whether or not attributed to study medication, will also be recorded in participant diary and CRF.
Serious adverse events (SAE's) will be followed up for the duration of the trial. Adverse events of special interest will be categorised as per CEPI guidelines (1).
Adverse reactions will be reported through the RCH immunisation service and escalated to the Victorian Specialist Immunisation Services.

8.3 Documentation of AEs

The AE will be described in the source documents (e.g., electronic or paper diary card) and captured on the CRF and will include:

- A description of the AE
- The onset date, duration, date of resolution
- Severity (mild, moderate, or severe– what is the impact on the participant's daily life?)
- Seriousness (i.e., is it an SAE?)
- Any action taken, (e.g., treatment, follow-up tests)
- The outcome (recovery, death, continuing, worsening)
- The likelihood of the relationship of the AE to the trial treatment (Unrelated, Possible, Probable, Definite)

Changes in the severity of an AE will be reported. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

8.4 Assessing the relatedness (causality) of a participant's AE

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The relationship of the event to the trial intervention will be graded/ assessed as follows:

Unrelated	Unlikely temporal relationship to study product. Alternate aetiology likely (clinical state, environmental or other interventions) and does not follow known typical or plausible pattern of response to study product
Possible	Reasonable temporal relationship to study product; or event not readily produced by clinical state, environmental or other interventions; or similar pattern of response to that seen with other vaccines
Probable	Reasonable temporal relationship to study product; and event not readily produced by clinical state, environment, or other interventions or known pattern of response seen with other vaccines
Definite	Reasonable temporal relationship to study product; and event not readily produced by clinical state, environment, or other interventions; and known pattern of response seen with other vaccines

8.5 Assessing the expectedness of a participant's AE

The severity of an Adverse Events will be graded/ assessed as follows:

Grade 0	None
Grade 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
Grade 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
Grade 4	Potentially Life-threatening: Requires assessment in A&E or hospitalisation

8.6 Reporting of safety events

Sponsor-Investigator Reporting Procedures

The Sponsor-Investigator must assess and categorise the Expedited Safety Reports received from Investigators and report these to all Site Principal Investigators, the approving HREC and TGA in accordance with the NHMRC's 'Safety monitoring and reporting in clinical trials involving therapeutic goods' (November 2016) and any additional requirements of the approving HREC. All safety reports must clarify the impact of the safety event on participant safety, trial conduct and trial documentation. The Sponsor-Investigator is responsible for the following reporting to PIs, the HREC(s) and TGA:

1. All SSIs that meet the definition of a USM within 72 hours of becoming aware of the issue.
2. All other SSIs within 15 calendar days of instigating or becoming aware of the issue
3. For SSIs leading to an amendment of trial documentation:
    a. Submit details of the SSI without undue delay and no later than 15 calendar days of becoming aware of the issue.
    b. Submit amendment to the HREC without undue delay.
4. For SSIs leading to temporary halt or early termination of a trial for safety reasons:

a. Communicate reasons, scope of halt, measures taken, further actions planned without undue delay and no later than 15 calendar days of decision to halt.
b. For a temporary halt, notify the PIs, HREC and TGA when the trial restarts, including evidence that it is safe to do so.

The Sponsor will also report SUSARs to the TGA as follows:

1. Fatal or life-threatening SUSARs immediately, but no later than 7 calendar days after being made aware of the issue (follow up info within a further 8 calendar days)
2. All other SUSARs no later than 15 calendar days of being made aware of the issue

The Sponsor is responsible for providing the additional safety information to the approving HREC:

1. Provide an annual safety report, including a summary of the evolving safety profile of the trial

The Sponsor is also responsible for providing any updated Product Information/Investigator's Brochure to Investigators.

9 DATA AND INFORMATION MANAGEMENT

The Principal Investigator is responsible for storing essential study documents relevant to data management and maintaining a site-specific record of the location(s) of the site's data management-related Essential Documents.

The Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants at their site. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring, and available. Changes to source data collected by MCRI must be traceable and explained in a note at relevant variables on the electronic case report form (eCRF). A site-specific Source Document Plan will be maintained to indicate the location(s) of source documents.

The Principal Investigator will maintain accurate data collection forms (known as case report forms - CRFs) and ensure that the collected and reported data is accurate, legible, complete, entered promptly, and enduring.

Any person delegated to collect data, perform data entry, or sign for data completeness will be recorded on the delegation log and trained to perform these study-related duties and functions.

Data generated for this study will be handled according to the relevant standard operating procedures (SOPs) and Data Management Plan (DMP). Full details of all processes are provided in a separate study-level DMP.

9.1 Data management

9.1.1 Data generation (source data)

Source documents are all documents used by the investigator that relate to the participant's medical history, that verify the existence of the participant, the inclusion and exclusion criteria, and all records covering the participant's participation in the study. They include but are not limited to

laboratory reports, memoranda, vaccination records, hospital records, and participant files. The site principal investigator is responsible for maintaining source documents.

An electronic CRF (eCRF) will be completed for all recruited participants.

In this study, the following types of data will be collected:

- Identifying personal information (contact details, dates of birth, home address and telephone contact and gender)
- Sensitive information, including health data (dates of COVID-19 vaccinations, medical history, primary COVID vaccine (Pfizer-BioNTech (BNT162b2, or *Comirnaty®*), AstraZeneca (ChAdOx1-S, or *Vaxzevria®*)); intervention vaccine (Pfizer-BioNTech (NT162b2, or *Comirnaty®*), Moderna (mRNA-1273, or Spikevax®))
- Reactogenicity information (pain, tenderness, erythema/redness, induration/swelling, fever, nausea/vomiting, headache, fatigue/malaise, myalgia, arthralgia
- Adverse events and serious adverse events
- Biological information (blood sample, immunologic assay results, including binding antibodies, functional antibodies, neutralizing antibodies, cellular immunity)

Source Document Plan

The source documents for this study include: COVID-19 vaccination details, date of birth, and sex); questionnaires completed by the participant and researcher (MCRI's eCRF).

A Source Document Plan will be maintained to document the source (i.e., original recording) for each data discrete item/category of items collected for the study. This Source Document Plan, signed and dated by the Principal Investigator, will be prepared before recruitment of the first participant and filed in the site's Investigator Site File.

9.1.2 Data capture methods and data use, storage, access, and disclosure during the trial

Data collection methods

Data capture and entry will be electronic. Data for this study will be collected and entered using electronic data collection forms, completed by authorised study staff and participants where applicable.

The following licensed research data collection tools will be used:

- Study data will be collected and managed using REDCap electronic data capture tools, hosted at MCRI. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. (12, 13)

- Data recorded will be linked by unique participant identifiers

Further details on the data variables are in the study DMP.

Use of the data

The data will be used for the analyses specified in the protocol and Statistical Analysis Plan (SAP).

Following the completion and analysis of the study, the data will be retained long-term following the mandatory archive period for use in future research projects.

Storage and access

Electronic data will be securely stored in MCRI's REDCap database system and in files stored in MCRI's network file servers, which are backed up nightly. Files containing private or confidential data will be stored only in locations accessible by appropriate designated members of the research team.

REDCap is hosted on MCRI infrastructure and is subject to the same security and backup regimen as other systems (e.g., the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. REDCap maintains an audit trail of data creation, update, and deletion events accessible to project users who are granted permission to view it. Access to REDCap will be provided via a REDCap user account created by the MCRI system administrator. The permissions granted to each user within each REDCap project will be controlled by and will be the responsibility of the study team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed before personnel commencing data entry on REDCap.

Authorised representatives of the sponsoring institution and representatives from the HREC, Research Governance Office, and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this study. The study site will permit access to such records.

Disclosure

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party without the prior written approval of the sponsoring institution. Clinical information will not be released without the participant's written permission, except as necessary for monitoring by the HREC, Research Governance Office, or regulatory agencies.

9.1.3 Data confidentiality

Participant confidentiality is strictly held in trust by the Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover the testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

To preserve confidentiality and reduce the risk of identification during collection, analysis, and storage of data and information, the following will be undertaken:

(1) The number of private/confidential variables collected for individual study participants has been minimised. The data collected will be limited to that required to address the primary and secondary objectives.

(2) Participant identifiers will be stored separately from the data collected, and documents with identifiers will be stored separately from participant data. Participant data and samples will be identified using a unique participant study number assigned to the study participant ("re-identifiable"). The Principal Investigator is responsible for storing a master file of names and other identifiable data with the participant ID; access to this document will be restricted to the site study team. The master file will be stored securely and separately from study data in locked/ password-protected databases with passwords kept separately. Age and sex will be included in the data; however, it is unlikely to make specific participants or families identifiable as identifiers will be stored separately.

Separation of the roles responsible for the management of identifiers and those responsible for analysis of content. The Principal Investigator will ensure access to the data is restricted, using REDCap's permission control functionality ("REDCap Users and Permissions").

9.1.4 Quality assurance

Data validity and quality assurance will be ensured by the following:

(1) Data collection and entry into the eCRF will be completed by authorised staff designated by the investigator. Appropriate training on eCRF completion will be conducted with the relevant investigator and all authorised staff before the study starts and any data is entered.

(2) All data will be entered in English. eCRFs are to be completed as soon as possible after each participant's visit. For information collected specifically for the study, data may be entered directly to the eCRF without duplicating the information across separate source documentation and eCRF. If data are unavailable or missing, this will be indicated on the eCRF. Changes or corrections made on eCRF will be tracked via an audit trail.

(3) Once the eCRFs have been entered, edit and consistency checks will be performed as outlined in the DMP. Data queries generated for logic and legality will be reviewed by authorised study staff for clarification. After resolving the queries, the responsible Data Manager will make the necessary updates to the database. An audit trail of all changes to the database will be maintained. Once all queries have been resolved, the database will be locked.

(4) The Principal Investigator will be required to sign off on the eCRF data before the final database lock.

(5) An audit is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated related activities were conducted. The data were

recorded, analysed, and accurately reported according to the protocol, study SOPs, GCP, and the applicable regulatory requirement(s).

Authorised representatives of MCRI, its designee, a regulatory authority, or the IEC may visit the centre to perform audits or inspections. The investigator should contact MCRI or designee immediately if a regulatory agency contacts them about an inspection at their centre. If an audit or inspection occurs, the site PI agrees to allow the auditor/inspector direct access to all relevant documents and allocate their staff's time to the auditor/inspector to discuss findings and any relevant issues.
The statistician will be provided with anonymised data, with participants identifiable only by unique participant study number/code. The statistician will analyse the de-identified data.

9.1.5 Archiving - Data and document retention

Archiving

The Investigator will take measures to prevent accidental or premature destruction of these documents. For this study, essential documents, and data (including biological samples) will be retained for a minimum of 7 (seven) years post-study.

The central study site and laboratory for this study are:

- New Vaccines Research Group, Infection & Immunity, Murdoch Children's Research Institute

Records will not be destroyed without the written consent of the Principal Investigator.

Destruction

After the archival period of 7 (seven) years, The Principal Investigator will take measures to ensure secure destruction of hardcopies of study data. Any hardcopy data will be disposed of via a confidential shredding process. Noting that simply deleting files does not destroy the information, electronic CRFs will be destroyed under guidance from MCRI IT to ensure the files are permanently deleted.

The electronic, anonymised database will not be destroyed
At the end of the archival period, eCRFs will be disposed of via secure destruction methods. Electronic databases will be retained by MCRI, stored on the secure server

9.1.6 Sample management: collection and storage

The study has been discussed with the biobanking team and a Biobanking Request Form has been submitted.

10 TRIAL OVERSIGHT

10.1 Governance structure

The Governance structure is outlined below.

10.1.1 Trial Management Group (TMG)

The Site Principal Investigator is responsible for supervising any individual or party to whom they have delegated tasks at the trial site. They must provide continuous supervision and documentation of their oversight. To meet this GCP requirement, a small group will be responsible for the day-to-day management of the trial and will include at a minimum the Site PI, project manager, data manager and

a representative from the Immunology team. The group will closely review all aspects of the conduct and progress of the trial, ensuring that there is a forum for identifying and addressing issues. Meetings must have minutes with attendees listed, pertinent emails retained, and phone calls documented.

10.1.2 Trial Steering Committee (TSC)

A TSC will be established to provide expert advice and overall supervision and ensure that the trial is conducted to the required standards. The TSC will meet at least annually, with more frequent meetings as needed, and will work to a Terms of Reference.

10.1.3 Safety Monitoring

Monitoring will be performed according to Good Clinical Practice (GCP) guidelines by external monitors. Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigator will provide direct access to all trial related source data/documents and reports for the purpose of monitoring.

Independent Safety Monitor

An Independent Safety Monitor will be responsible for providing independent safety monitoring in a timely fashion. The Independent Safety Monitor will operate within agreed terms of reference and will provide input to the trial investigators.

Independent Data Safety Monitoring Board (DSMB)

Safety oversight will be under the direction of a DSMB. The DSMB will meet at least 6 monthly to review SAEs or AEs deemed possibly, probably or definitively related to study interventions. The DSMB will make recommendations concerning the conduct, continuation or modification of the study for safety reasons. The DSMB will meet virtually prior to the commencement of the trial then again on at least 2 occasions to review the one-month immunogenicity data for the standard and fractional-dose recipients, and to review the 6 months data. The DSMB will decide whether a fourth dose is required, based on up-to-date safety data, for participants who received a fractional dose and did not mount an adequate antibody response. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organisational meeting of the DSMB. The DSMB will be chaired by an experienced vaccine trial specialist and will contain one statistician, one adult physician and representatives from Indonesia and Mongolia. Members of the DSMB will be independent of trial conduct.

10.2 Site Monitoring

Trial site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol and amendment(s), good clinical practice and applicable regulatory requirements.

Full details of trial site monitoring are documented in the Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Monitoring for this trial will be performed by one of the three trial managers. The monitoring will take place on-site. The monitors will review 100% of original signed consent forms, trial eligibility data and data related to primary outcome, safety and other key data variables; review of all withdrawals from trial; targeted review of other data including investigational vaccine administration and accountability.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.3 Quality Control and Quality Assurance

Both the Sponsor-Investigator and Site Investigator have responsibilities in relation to quality management.

The Sponsor-Investigator will develop SOPs that identify, evaluate and control risk for all aspects of the trial, e.g., data management, training, eligibility, informed consent and adverse event reporting. The Sponsor-Investigator will also implement quality control (QC) procedures, which will include the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the study staff for clarification/resolution.

As outlined in the previous section (Site Monitoring), the trial monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, good clinical practice and applicable regulatory requirements.

In the event of non-compliance that significantly affects human participant protection or reliability of results, the Sponsor-Investigator will perform a root cause analysis and corrective and preventative action plan (CAPA).

In addition, the clinical site will perform internal quality management of trial conduct, data and biological specimen collection, documentation and completion.

11 STATISTICAL METHODS

11.1 Sample Size Estimation

Sample size calculations were performed using nQuery 8 software. Precision-based sample size calculations were performed based on the reactogenicity outcomes. Assuming the percentage of participants reporting local or systemic reactions is 50%, 100 participants will produce a confidence interval that is 9.8 percentage points from the observed percentage. For immunogenicity, sample size calculations were based on the comparison of seroresponse rates between the standard and fractional dose groups within the non-inferiority framework. Assuming a -10% non-inferiority margin and a seroresponse rate of 95% in both groups, the study will have 90% power for the non-inferiority comparisons using 100 participants per group. If we make the more conservative assumption that the seroresponse rate is lower in the fractional-dose group (93% versus 95% seroresponse), then 100 per group will provide 66% power.

11.2 Population to be analysed

Analysis of this trial is planned on both the intention-to-treat population (ITT), with all participants to be analysed in the group they were randomised to, as well as on the per-protocol (PP) population, consisting of participants who adhered to the study protocol . However, it is expected that withdrawn participants may not have data to contribute at all time points as blood samples may not be collected after the time of their withdrawal.

11.3 Methods of analysis

Reactogenicity following immunisations will be presented as the number and percentage of participants self-reporting local reactions (pain; tenderness, redness; swelling at or near the injection site) and systemic reactions (fever, nausea/vomiting, headache, fatigue/malaise, myalgia), and the severity of

these reactions (mild, moderate, severe, life-threatening or fatal). Reactogenicity data will be presented separately by group and time point.
For immunogenicity, antibody levels will be presented as geometric mean titres (GMT) with 95% confidence intervals. Changes from baseline will be expressed as geometric mean fold ratios (GMFR), calculated as the ratio of the post-booster GMT to the baseline GMT. Seroresponse will be defined as a ≥4-fold rise in post-booster antibody levels compared to baseline (or ≥2-fold rise if the baseline (pre-booster) antibody level was ≥200 BAU/ml). To assess the non-inferiority of the fractional dose compared with the standard dose, comparisons will be based on the difference in percentage of participants with seroresponse. Using a non-inferiority margin of -10% (fractional-dose minus standard dose), non-inferiority will be declared if the lower limit of the 95% confidence interval around the difference in percentages is greater than -10%, where confidence intervals are calculated using Score-based methods (14)
Analyses will be performed using Stata software (15). Detailed methodology will be outlined in a separate Statistical Analysis Plan.

Primary outcome (All samples at all timepoints)

The binding IgG data using the Euroimmun S1 IgG ELISA kits will be reported as relative units/ml (RU/ml) as per manufacturer's instructions. A result of <8 RU/ml: negative (IgG Antibodies for SARS-CoV-2 are not detected), ≥8 to <11 RU/ml: borderline (IgG antibodies is indeterminate/equivocal with this sample, ≥11 RU/ml: positive (IgG antibodies for SARS-CoV-2 are detected). Conversion to binding antibody units (BAU/ml) will also be done using the WHO reference serum from NIBSC, UK. Data will be presented as geometric mean titresand 95% confidence intervals.

Analysis comparing fractional and standard dose groups will be based on seroresponse rate (SRR) at 28 days post study vaccine, defined as:
• ≥4-fold rise in GMCs at 28 days post study vaccine from baseline among subjects with no pre-dose (<200 BAU/ml) detectable titres
•≥ 2-fold rise in GMCs at 28 days post study vaccine among subjects with baseline titre of >200 BAU/ml pre-booster

Secondary outcomes

Functional antibody (all samples at all timepoints) – for the C-PASS assay (sVNT), data is reported as percentage (%) inhibition by neutralising antibodies using the manufacturer's instructions. A <30% inhibition is considered negative while ≥30% inhibition is considered positive. Data will be presented as mean and standard deviation.

Neutralizing assay (20% subset of samples at all timepoints) – Data will be reported as endpoint titre calculated using the Reed/Muench method (16). A titre of 10 reflects undetectable neutralizing activity.

Cellular immunity: (on a 40% subset at three timepoints – baseline, 1 month and 12 months)

Quantiferon COVID IFNγ release assay – Levels of IFNγ will be reported in IU/ml according to manufacturer's instructions. Data will be reported as GMC and 95% confidence intervals.

IFNγ Elispot – The number of IFNγ producing cells/million PBMCs will be reported using means and 95% confidence intervals.

Intracellular cytokine staining – The data will be reported as frequency (%) of cytokine-expressing T cells (e.g. total T cells, CD4 T cells, CD8 T cells). Cytokines such as IFNγ (Th1) and IL-5 (Th2) will be measured as a minimum. This will be presented as means and 95% confidence intervals.

Multiplex cytokine assays – A 10-plex panel of cytokines will be measured in supernatants from the Elispot studies. Levels of cytokine concentrations will be reported in pg/ml and data presented as GMC and 95% confidence intervals.

11.4 Interim Analyses

We will conduct an interim analysis of the antibody responses after one month to ensure that the responses in the fractional dose groups are adequate. This will be assessed on both individual and group levels by the DSMB. If fractional dose responses are considered inadequate an appropriate rescue strategy will be developed, probably involving a single dose of the vaccine in question at 3 months. If the fractional dose is considered inadequate this information will be made public and shared specifically with WHO and other groups working in the field. In addition, an analysis will be undertaken once all data are collected for the 6 months analysis to review the potential need for policy changes. All such analyses will be undertaken by the trial statistician, Dr Cattram Nguyen.

12 ETHICS AND DISSEMINATION

12.1 Research Ethics Approval & Local Governance Authorisation

This protocol, the informed consent document, and any subsequent amendments will be reviewed and approved by the human research ethics committee (HREC) before the research. A letter of protocol approval by HREC will be obtained before the commencement of the trial and approval for other trial documents requiring HREC review.

12.2 Amendments to the protocol

This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participant's willingness to continue participation in the trial is considered an amendment and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC for approval before being implemented.

12.3 Protocol Deviations and Serious Breaches

All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the Site Principal Investigator, who will assess for seriousness.

Those deviations deemed to affect to a significant degree the rights of a trial participant or the reliability and robustness of the data generated in the clinical trial will be reported as serious breaches. Reporting will be done promptly (Site Principal Investigator to report to the Sponsor-Investigator within 72 hours and to the Site RGO within seven days; Sponsor-Investigator to review and submit to the approving HREC within seven days).
Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken, and a corrective and preventative action plan prepared.
Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

13 CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover the testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.
The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorised third party without the prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.
All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the Participant Identification Number (SID) to maintain participant confidentiality.
Clinical information will not be released without the participant's written permission, except as necessary for monitoring by HREC or regulatory agencies.

14 PARTICIPANT REIMBURSEMENT

Study participants will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses.

15 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

No conflict of interests.

16 DISSEMINATION AND TRANSLATION PLAN

Information generated by the trial will be shared at 3 levels. Participants will be given access to their personal antibody levels and to the analysed data at each of the time points once it becomes available. The former will be on special request only, while the latter will be provided by group email as the analysed antibody data becomes available.

Interim analysis will be prepared from reactogenicity and one month immunogenicity data. These analyses will be presented to CEPI and WHO and shared with the authorities in Australia as soon as available. This will represent the first publication.

At the completion of the study a major publication will be prepared for an international journal. The data will also be presented at appropriate international conferences and meetings.

17 ADDITIONAL CONSIDERATIONS

Not applicable.

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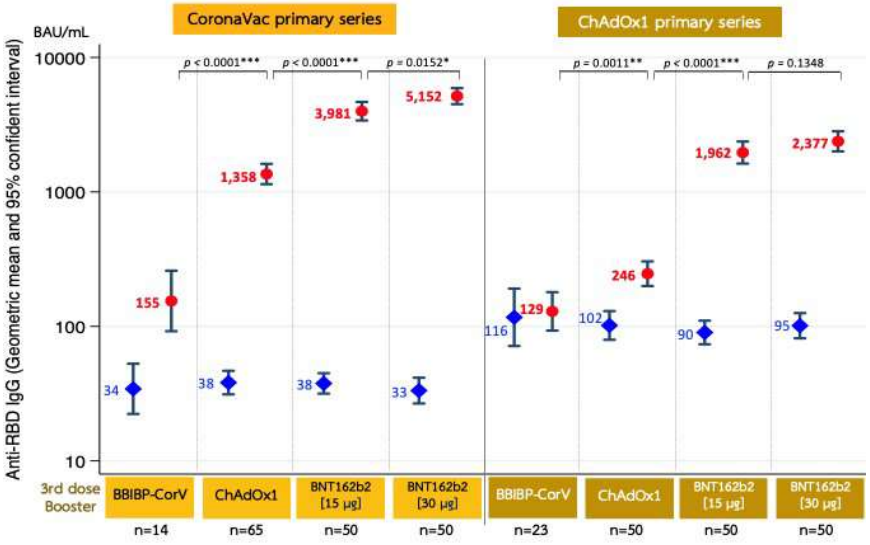
19 APPENDICES

APPENDIX 1 – Pfizer half dose booster data from Thailand, courtesy of Dr Kulkanya Chokephaibulkit, MD, Professor of Pediatrics, Director, Siriraj Institute of Clinical Research (SICRES), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

The Preliminary Report: Safety and Immunological Response of Heterologous Booster COVID-19 Vaccination following the Primary Series of CoronaVac and ChAdOx1 (3rd Dose Booster)



Inactivated vaccine or homologous platform is not an effective booster

-Among subjects who received 2-dose CoronaVac (inactivated vaccine), a boosting with ChAdOx1 or BNT162b2 provided high GM levels
-Among subjects who received 2-dose ChAdOx1, a boosting with BNT162b2 provided high GM levels
-Half dose of BNT162b2 induced high titers not different from full dose

The Preliminary Report: Safety and Immunological Response of Heterologous Booster COVID-19 Vaccination following the Primary Series of CoronaVac (3rd Dose Booster)

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SiCRES

Rationale: The inactivated COVID-19 vaccine manufactured by Sinovac (CoronaVac) has been widely used in Thailand. The emergence of Delta variant that spread quickly, together with the report of breakthrough infections raises the concern of immunity induced by CoronaVac. Our previous report revealed low geometric mean PRNT50 titer (24.28) against Delta variant after 2-dose CoronaVac injections. From August 2021, a third dose booster has been recommended in frontline healthcare workers in Thailand who have received 2 doses of CoronaVac. We investigated the immunogenicity of a booster vaccination by heterologous platform vaccine, in particular neutralizing antibody against the Delta

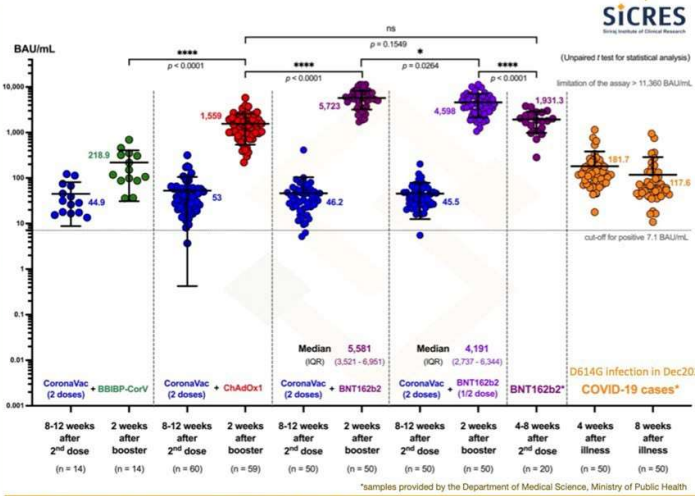

Figure 1. Quantitation of anti-SARS-CoV-2 RBD IgG determined by CMIA

APPENDIX 2 – Product information sheets

Product information sheet - Moderna.pdf

Product information sheet - Pfizer.pdf